5 **Schieve LA**, Meikle SF, Ferre C, Peterson HB, Jeng G, Wilcox LS. Low and very low birth weight in infants conceived with use of assisted reproductive technology. *N Engl J Med* 2002;**346**:731–7.
6 **Cox GF**, Burger J, Lip V, Mau UA, Sperling K, Wu BL. Intracytoplasmic sperm injection may increase the risk of imprinting defects. *Am J Hum Genet* 2002;**71**:162–64.
7 **Orstavik KH**, Eiklid K, van der Hagen CB, Spetalen S, Kierulf K, Skjeldal O, Buiting K. Another case of imprinting defect in a girl with Angelman syndrome who was conceived by intracytoplasmic semen injection. *Am J Hum Genet* 2003;**72**:218–19.
8 **Maher ER**, Brueton LA, Bowdin SC, Luharia A, Cooper W, Cole TR, Macdonald F, Sampson JR, Barratt CL, Reik W, Hawkins MM. Beckwith-Wiedemann syndrome and assisted reproduction technology (ART). *J Med Genet* 2003;**40**:62–4.
9 **DeBaun MR**, Niemitz EL, Feinberg AP. Association of in vitro fertilization with Beckwith-Wiedemann syndrome and epigenetic alterations of LIT1 and H19. *Am J Hum Genet* 2003;**72**:156–60.
10 **Gicquel C**, Gaston V, Mandelbaum J, Siffroi JP, Flahault A, Le Bouc Y. In vitro fertilization may increase the risk of Beckwith-Wiedemann syndrome related to the abnormal imprinting of the KCN1OT gene. *Am J Hum Genet* 2003;**72**:1338–41.
11 **Lossie AC**, Whitney MM, Amidon D, Dong HJ, Chen P, Theriaque D, Hutson A, Nicholls RD, Zori RT, Williams CA, Driscoll DJ. Distinct phenotypes distinguish the molecular classes of Angelman syndrome. *J Med Genet* 2001;**38**:834–45.
12 **Zeschnigk M**, Lich C, Buiting K, Doerfler W, Horsthemke B. A single-tube PCR test for the diagnosis of Angelman and Prader-Willi syndrome based on allelic methylation differences at the SNRPN locus. *Eur J Hum Genet* 1997;**5**:94–8.
13 **Basso O**, Weinberg CR, Baird DD, Wilcox AJ, Olsen J. Subfecundity as a correlate of preeclampsia: a study within the Danish National Birth Cohort. *Am J Epidemiol* 2003;**157**:195–202.
14 **Henriksen TB**, Baird DD, Olsen J, Hedegaard M, Secher NJ, Wilcox AJ. Time to pregnancy and preterm delivery. *Obstet Gynecol* 1997;**89**:594–9.
15 **Pandian Z**, Bhattacharya S, Templeton A. Review of unexplained infertility and obstetric outcome: a 10 year review. *Hum Reprod* 2001;**16**:2593–7.
16 **Helmerhorst FM**, Perquin DA, Donker D, Keirse MJ. Perinatal outcome of singletons and twins after assisted conception: a systematic review of controlled studies. *BMJ* 2004;**328**:261.
17 **Miozzo M**, Simoni G. The role of imprinted genes in fetal growth. *Biol Neonate* 2002;**81**:217–28.
18 **Ertzeid G**, Storeng R. The impact of ovarian stimulation on implantation and fetal development in mice. *Hum Reprod* 2001;**16**:221–5.
19 **Niemitz EL**, Feinberg AP. Epigenetics and assisted reproductive technology: a call for investigation. *Am J Hum Genet* 2004;**74**:599–609.

ECHO

Further evidence of genetic heterogeneity in familial exudative vitreoretinopathy; exclusion of *EVR1*, *EVR3*, and *EVR4* in a large autosomal dominant pedigree

C Toomes, L M Downey, H M Bottomley, H A Mintz-Hittner, C F Inglehearn

Please visit the *Journal of Medical Genetics* website [www.jmedgenet.com] for a link to the full text of this article.

Background/aims: Familial exudative vitreoretinopathy (FEVR) is an inherited blinding condition characterised by abnormal development of the retinal vasculature. The aim of this study was to perform linkage analysis in a large family affected with FEVR to determine whether the mutation involved was in one of the three known autosomal dominant FEVR loci or in another as yet unidentified gene.

Methods: Genomic DNA samples from family members were polymerase chain reaction (PCR) amplified with fluorescently tagged microsatellite markers spanning the *EVR1/EVR4* locus (11q13-14) and the *EVR3* locus (11p12-13). The resulting PCR products were resolved using an automated DNA sequencer and the alleles sized. These data were used to construct haplotypes across each locus and linkage analysis was performed to prove or exclude linkage.

Results: The clinical evaluation in this family suggested features typical of FEVR, with deficient peripheral retinal vascularisation being the common phenotype in all affected individuals. However, linkage analysis proved that this family has a form of FEVR genetically distinct from the *EVR1*, *EVR3* and *EVR4* loci.

Conclusion: The exclusion of linkage in this family to any of the known FEVR loci proves the existence of a fourth locus for autosomal dominant FEVR and shows that this rare disorder is far more heterogeneous than previously thought.

▲ *British Journal of Ophthalmology* 2005;**89**:194–197.